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Functional Mapping of the Human Auditory Cortex: fMRI Investigation of a Patient with Auditory Agnosia from Trauma to the Inferior Colliculus

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Objective: To use functional magnetic resonance imaging to map the auditory cortical fields that are activated, or nonreactive, to sounds in patient M.L., who has auditory agnosia caused by trauma to the inferior colliculi.

Background: The patient cannot recognize speech or environmental sounds. Her discrimination is greatly facilitated by context and visibility of the speaker's facial movements, and under forced-choice testing. Her auditory temporal resolution is severely compromised. Her discrimination is more impaired for words differing in voice onset time than place of articulation. Words presented to her right ear are extinguished with dichotic presentation; auditory stimuli in the right hemifield are mislocalized to the left.

Methods: We used functional magnetic resonance imaging to examine cortical activations to different categories of meaningful sounds embedded in a block design.

Results: Sounds activated the caudal sub-area of M.L.'s primary auditory cortex (hA1) bilaterally and her right posterior superior temporal gyrus (auditory dorsal stream), but not the rostral sub-area (hR) of her primary auditory cortex or the anterior superior temporal gyrus in either hemisphere (auditory ventral stream).

Conclusions: Auditory agnosia reflects dysfunction of the auditory ventral stream. The ventral and dorsal auditory streams are already segregated as early as the primary auditory cortex, with the ventral stream projecting from hR and the dorsal stream from hA1. M.L.'s leftward localization bias, preserved audiovisual integration, and phoneme perception are explained by preserved processing in her right auditory dorsal stream.

Key Words: auditory agnosia, sound recognition, functional imaging, auditory cortex, inferior colliculus

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BOLD = blood-oxygen-level-dependent. **fMRI** = functional magnetic resonance imaging. **ke** = extent threshold. **MRI** = magnetic resonance imaging. **STG** = superior temporal gyrus. **T** = height threshold.

Robert Rafal's remembrance of Dr Oscar Marin appears earlier in this issue.

Since the mid-1990s, evidence has emerged for distinct structural and functional regions within the auditory cortex (Kaas and Hackett, 2000; Petkov et al, 2006). In a primate model, Kaas and Hackett (2000) described a three-layered hierarchical structure with core auditory fields projecting to belt and then parabelt auditory fields. In humans, histologic staining showed two auditory fields in the primary auditory cortex in Heschl gyrus (Sweet et al, 2005; Wallace et al, 2002). High-resolution functional magnetic resonance imaging (fMRI) tonotopic mapping has confirmed homologies of these core auditory fields with the monkey auditory fields (Da Costa et al, 2011; Humphries et al, 2010; Langers and van Dijk, 2012; Striem-Amit et al, 2011). These studies demonstrated homology between the anterior bank of Heschl gyrus in humans and monkey area R (designated as area hR in humans), and homology between the posterior bank of Heschl gyrus in humans and monkey area A1 (designated as area hA1 in humans).

While anatomically discrete auditory fields have been demonstrated outside the primary auditory cortex in the human brain (Fullerton and Pandya, 2007; Rivier and Clarke, 1997; Wallace et al, 2002), our knowledge of their functional organization is limited. Critically, little is known about how damage to individual auditory fields contributes to auditory deficits in patients with aphasia or auditory agnosia.

Auditory agnosia is a rare disorder in which people can detect sounds but are impaired in recognizing, repeating, and mimicking them. Despite their auditory deficit, these people have intact speaking, reading, and writing abilities and unimpaired overall linguistic and cognitive performance.

In the majority of patients, auditory agnosia is caused by cortical pathology. Because the lesions causing

the syndrome are typically large and do not respect the boundaries of individual auditory fields, much remains to be learned about the neuroanatomic substrates and about patients' perceptual experience (Phillips and Farmer, 1990; Poeppel, 2001).

Here we report patient M.L., who suffered damage to the auditory pathways in her brainstem. A traumatic head injury caused a hemorrhage in her dorsal midbrain, affecting the left inferior colliculus and its brachium. This lesion led to partial de-afferentation of her medial geniculate nucleus and auditory cortex, especially on the left side. Her chief residual disability was a profound auditory agnosia for both speech and environmental sounds.

Although brainstem auditory agnosia has not been given an official name, some authors have referred to the condition as *midbrain deafness* (Sloane, 1943; Vitte et al, 2002).

Auditory agnosia caused by a circumscribed inferior colliculus lesion is extremely rare, with only nine cases reported to date (see Supplemental Digital Content 1, <http://links.lww.com/CBN/A63>). By systematically comparing these rare patients' symptoms with those of patients with auditory agnosia caused by cortical damage, we can both extend our understanding of the pathophysiology of auditory agnosia and further illuminate the neural basis of hearing.

With these goals in mind, we used fMRI to measure how M.L.'s intact but partially deafferented auditory cortex reacted to sound.

To the best of our knowledge, this study is the first report of auditory cortical activation in a patient with auditory agnosia who is impaired in both speech and environmental sounds. However, we should note two relevant earlier studies: Engelen et al (1995) described the activation pattern in a patient who had recovered from auditory agnosia, and Saygin et al (2010) described the activation pattern in auditory agnosia specific for environmental sounds.

As M.L.'s auditory cortex remained unscathed, we were able to document her auditory fields that were reactive (or unresponsive) to sounds. By correlating this cortical activation pattern with her performance on auditory perception tasks, we offer unique insights into the functional organization of the auditory cortex as well as the relationship between individual auditory fields and specific perceptual and comprehension deficits.

CASE REPORT: EARLY EVALUATIONS

Patient M.L., now 28 years old, came under the neurologic care of author R.D.R. after she sustained a severe closed head injury (Glasgow Coma Scale = 3) (Teasdale and Jennett, 1974) in a traffic accident at age 17. A computed tomography scan taken just after the accident revealed a hemorrhage in her right basal ganglia and left dorsal midbrain (Figure 1A).

M.L. remained in a vegetative state for almost 3 months. When she awoke, her hearing was severely impaired

but she was able to carry on a conversation with her relatives if they spoke slowly and she could see their faces.

By 4 months after the accident, M.L. was oriented to place, time, and her circumstances. She was initiating conversations and speaking in full sentences.

Five months after the accident, she was ambulatory, independent in daily activities, and able to return home to live with her parents.

Age 18: Audiologic Assessment

M.L. underwent audiologic assessments 8 and again 9 months after her accident. According to the audiologist's notes from those testing sessions, M.L.'s parents reported that she would not respond when called from another room, but seemed to react to the telephone ringing. She "did not report tinnitus or hyperacusis." Her speech was "distorted and slow" and she was "aware that her own speech had changed."

Otосcopy was normal in both ears. Tympanometry revealed normal compliance and normal middle ear pressure in both ears. Oto-acoustic emissions (transient evoked oto-acoustic emissions and distortion product oto-acoustic emissions) were normal in both ears, suggesting that M.L. had largely normal middle and inner ear function.

The testing audiologist reported that M.L.'s responses during pure-tone audiometry were "variable and inconsistent" and that she reported "being confused about whether she was hearing sounds or not." Pure-tone audiometry suggested severe asymmetric hearing loss, especially for low frequencies, and much worse for sounds presented to the right ear (Figure 2, left graph). Atypically, she was much better at detecting narrow-band sounds than pure tones, especially in the right ear.

A brainstem auditory evoked response test performed at 85 dB (normal hearing level) revealed normal latencies for waves I and III in both ears (Table 1). Wave V was absent after right ear stimulation and delayed after left ear stimulation. Threshold auditory evoked responses revealed no evoked potentials at 70 dB or lower in either ear.

M.L.'s speech perception was tested with a three-alternative forced-choice speech test. She was consistently able to identify which of three words was spoken, with no lipreading. On an open-ended sentence test with no lipreading, she was able to detect a voice speaking, but could not understand any of the words. A test using open-set single words had similarly poor results. When tested using open-set sentences with access to lipreading, she scored slightly better, but still got <20% of the words correct.

Age 19: Audiologic Assessment

At age 19, M.L. was tested again on her ability to discriminate words and environmental sounds. At that time, she could not report reliably whether a sound that she heard was a word spoken by a human voice. She could not identify speakers by their voices. When asked whether a speaker was her father or mother in a two-alternative forced-choice test, she answered correctly.

However, she acknowledged that she was basing her choice on pitch.

Age 20: Overall Status

Three years after the accident, M.L. was living a full and active life, going out with her friends and taking her dog for walks on the beach by her home. She had a job taking orders for drinks in the bar of a family-owned resort. Family and friends had not noted any change in her intellect or personality, and felt that her memory was good.

Her main persisting complaint was an inability to hear. She was also aware that the sound of her speech had changed. Her parents reported that, except for rare occasions when she responded to a ringing telephone, she generally did not respond to sounds that were outside the room where she was or were generated by people or objects out of her sight. She did not react to loud noises like jet planes flying close overhead.

Age 24: Neurologic and Limited Neuropsychological Evaluations

When M.L. was 24, her mental status was lucid. She was invariably attentive, engaged, and appropriate in her interactions. While at times she aborted tasks out of frustration, she was able to sustain effort and concentration. Her conversation showed good recall of current and recent events.

Between her hearing loss and motor impairments that affected her physical speed, an extensive battery of formal psychometric tests would not have been valid or useful. Nonetheless, she showed intact cognition on three commonly used tests (Mitrushina et al, 2005). We gave her a modified digit span, presenting the digits in written form, one at a time; her span was five forward and four backward. Her verbal fluency (F-A-S test) was in the 10th percentile. On the Trail Making Test (Army Individual Test Battery, 1944), the ratio of Part A to Part B was < 50%, which is in the normal range.

Neurologic examination revealed no ptosis or lid retraction and no pupillary abnormality. She had conspicuous macro-square wave jerks. Her eye movements were full, but with attempted vertical gaze (downward more than upward) there was convergence spasm. She had no weakness of her facial or pharyngeal muscles, and she did not have apraxia of speech. Her speech was intelligible, though dysphonic and slightly dysarthric. The quality of her speech was similar to that produced by individuals with hearing loss who cannot monitor the sound of their own voice.

She had an action tremor in the right arm. She showed no weakness of the arms or legs, but she walked with a somewhat spastic gait, tending to circumduct the right leg. Her tendon reflexes were increased on the right, especially in the arm. She had no clonus or spasticity, and her plantar responses were normal. She had no visual or tactile extinction. She was unsteady when trying to stand with her eyes closed and her feet together. Her postural reflexes were particularly impaired if perturbed backward.

Age 27: Pure-Tone Audiometry and Diagnostic Dilemmas

M.L.'s performance on pure-tone audiometry at age 27 was similar to that at age 18. As shown in the right graph of Figure 2, her sound detection remained severely impaired, especially in the right ear.

As with her earlier test, her performance this time was variable and unreliable. She was asked to raise her hand whenever she heard a click. After several trials, she removed the headphones and said that she did not hear any clicks, "just sounds...like someone whistling." She also reported that she found the detection task difficult because the tones were hard to distinguish from the "tunes in my head." She could not further characterize these "tunes," but said that they were not specific musical songs that she could recognize.

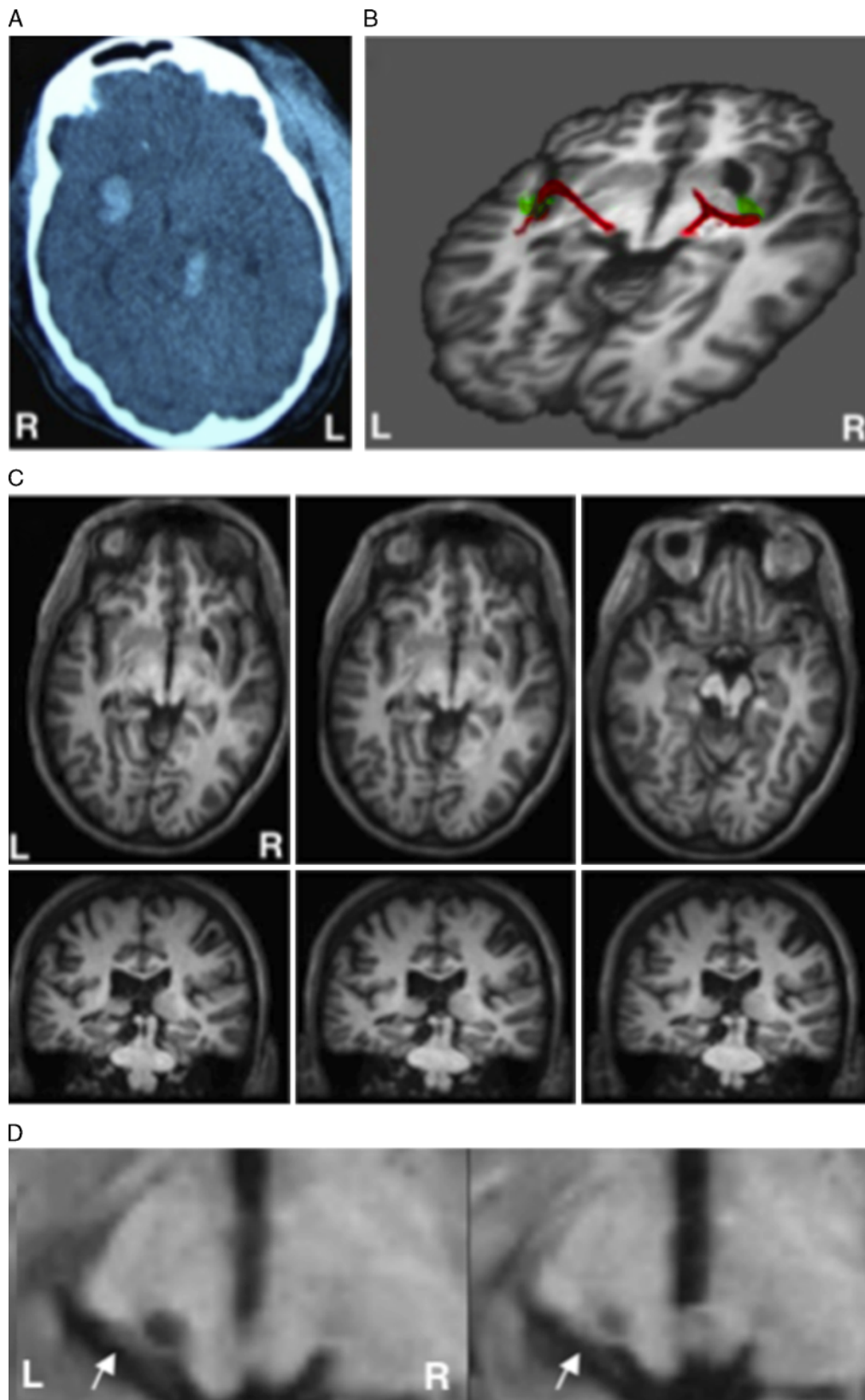
FIGURE 1. Anatomy of patient M.L.'s brain lesions.

Panel A: Age 17: Axial section from computed tomography scan taken at the time of her injury shows hemorrhages in the ventral basal ganglia in the right hemisphere and in the dorsal midbrain. The slice is viewed from below (radiologic orientation), so that structures on the left side of the brain appear on the right side of the image.

Panel B: Age 28: Probabilistic tractography using FSL FDT (FMRIB Diffusion Toolbox) (Behrens et al, 2003, 2007; <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki>). We collected diffusion-weighted echo-planar magnetic resonance images (MRI) at $1.5 \times 1.5 \times 1.5$ mm resolution. We scanned from 1000, 32, and 0 (baseline) isotropically distributed diffusion-encoding directions (*b* values), repetition time = 2 seconds, and echo time = 35 msec. For the probabilistic tractography, we manually marked the starting region (ie, drew seed masks) on Heschl gyrus (green regions) and the target region (waypoint mask) on the inferior colliculus (not shown in the figure). We then calculated the most probable streamline (hypothetical tract) between the two regions (red areas).

Panel C: Age 28: High-resolution ($0.7 \times 0.7 \times 0.7$ mm voxels) T1-weighted MRI scan obtained with a 3T Philips Achieva scanner (Philips Healthcare). Top row: Axial sections from ventral (right) to dorsal (left). The images are viewed from above (anatomic orientation), so that structures on the left side of the brain appear on the left side of the image. Bottom row: Coronal sections from posterior (right) to anterior (left), in anatomic orientation.

Panel D: Age 28: Two axial slices through the dorsal midbrain of the same high-resolution T1-weighted MRI shown in Panel C, in anatomic orientation. These images show that the lesion on the left encroaches on the anteromedial border of the medial geniculate (arrows), but does not damage it. The probabilistic tractography shown in Panel B confirmed normal connectivity between the medial geniculate and auditory cortex. L = left. R = right.



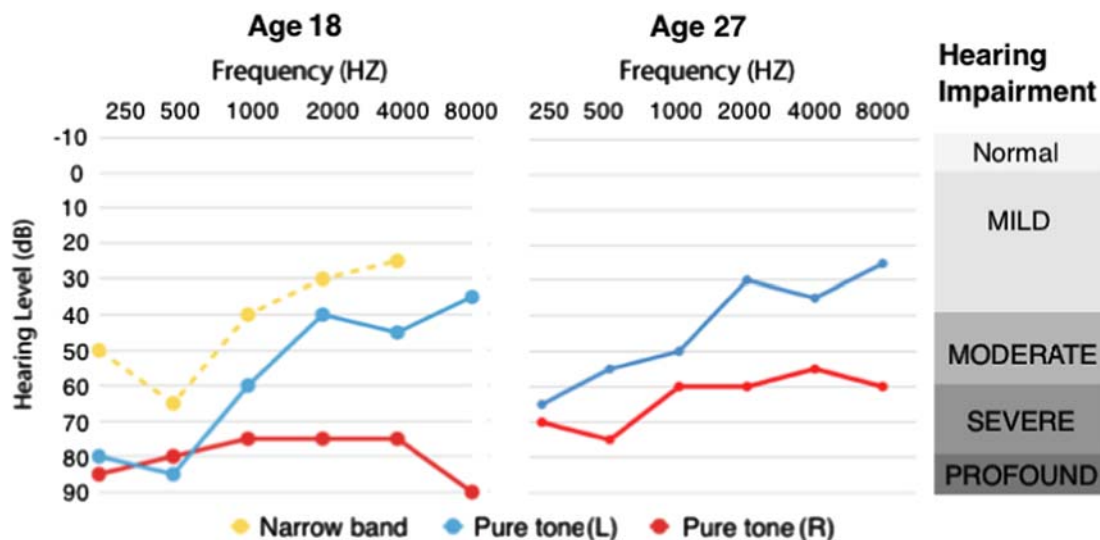


FIGURE 2. M.L.'s audiometry results at ages 18 and 27. Level of hearing impairment is displayed on the right, as measured by the decibel level of sound required for detection. For pure tones presented solely to the right ear, M.L.'s impairment was severe to profound at age 18, and moderate to severe 9 years later. For pure tones presented solely to the left ear, her impairment at both ages was severe for low tones and mild to moderate for higher tones. For narrow-band sounds presented to both ears, her impairment was moderate to mild. L = left. R = right.

M.L.'s performance on her two pure-tone audiometry tests, at ages 18 and 27, suggested severe asymmetric hearing loss, especially in her right ear. Acoustic reflexes, however, indicated intact cochlear function and were not consistent with such severe hearing loss. Moreover, her hearing thresholds were much lower when tested with narrow-band sounds and more complex stimuli such as words. We will return to this issue in the *Discussion* section, but we note here that her behavior during the testing clearly showed that her poor performance on pure-tone audiometry did not accurately reflect her auditory capabilities.

For all hearing tests that we conducted, the examiner invited M.L. to adjust the headphone volume to a comfortable level. Consistently, the volume that she chose was much the same as what the examiner (or control participants) would have chosen for themselves.

Also of note, at this stage in our evaluation we could not attribute the asymmetry between her left and right ears in pure-tone audiometry to pathology in the right cochlea, auditory nerve, or cochlear nucleus. Neither did she have evidence of any pathology in the peripheral auditory system or central auditory system (below the inferior colliculi) that could account for her asymmetry. Finally, our attempts to learn the cause of her raised hearing thresholds, particularly in the right ear, were confounded by the fact that this patient with pathology of the central nervous system was having auditory experiences, which she called "tunes in my head," that might be interfering with her detection by reducing the signal-to-noise ratio.

Ages 27 and 28: Anatomic Findings on MRI

M.L. underwent magnetic resonance imaging (MRI) (Figure 1C) twice, first at age 27 and again a year later as

part of an fMRI scan. We did not see changes between the two scans. They showed a cystic cavity in the right putamen at the site of her previous hemorrhage. She had a small periventricular lesion on the right lower pons, in the region of the inferior cerebellar peduncle, with some hemosiderin staining (a sign of previous hemorrhage) evident on T2-weighted images (not shown). She had nearly complete avulsion of the left inferior colliculus, sparing only its most medial and caudal parts. The MRI scan also showed destruction of the brachia of the superior and inferior colliculi, with the lesion extending ventrally into the red nucleus and laterally encroaching on the medial border of the left medial geniculate nucleus (Figure 1D).

Probabilistic tractography confirmed that M.L. had preserved bilateral thalamic connectivity to the auditory cortex (Figure 1B). We computed fractional anisotropy measurements for the streamlines connecting her inferior colliculus and auditory cortex on the left and right, using

TABLE 1. Patient M.L.'s Brainstem Auditory Evoked Response Latencies (msec) at Age 18, About 8 Months After Her Injury

	Left Ear	Right Ear
Wave I peak latency	1.68*	1.74*
Wave III peak latency	3.72*	3.68*
Wave V peak latency	7.46	None
I-III interpeak interval	2.04	1.94
III-V interpeak interval	3.74	Not applicable
I-V interpeak interval	5.78	Not applicable

*Normal.

the FSLstats utility of the FSL (FMRIB [Functional Magnetic Resonance Imaging of the Brain] Software Library) (FMRIB, Oxford, United Kingdom; <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki>).

We compared her results to those analyzed from 12 control participants, six men and six women, with an age range of 19 to 32. They had been recruited from Bangor University's undergraduate psychology program for a separate study (Rafal et al, 2015) and did not take part in the current study. These controls had given written consent conforming to standards of the Declaration of Helsinki.

We found that the mean fractional anisotropy values of the connections in M.L.'s left hemisphere (mean = 0.447) and right hemisphere (mean = 0.423) were no different from those of the controls (mean = 0.455, standard deviation = 0.12). The difference in fractional anisotropy values between M.L.'s left and right hemispheres (0.02) was also similar to that in the controls (mean = 0.01, standard deviation = 0.003).

Ages 27 and 28: Purpose of Auditory Perception Testing and fMRI Study

In the next two sections of the paper, we describe a battery of auditory perception tests and an fMRI study that we conducted with M.L. at ages 27 and 28. The purpose of the behavioral tests was to confirm that her symptoms are equivalent to those described in the literature for patients who had auditory agnosia caused by cortical damage. Once we confirmed this similarity, we took advantage of M.L.'s intact auditory cortex to give her an fMRI scan while she listened passively to sounds. The scan enabled us to identify the impaired auditory field that kept her from understanding sounds.

AGES 27 AND 28: ASSESSMENT OF AUDITORY PERCEPTION

Patients with auditory agnosia caused by cerebral damage have been studied almost exclusively with behavioral tests of such auditory faculties as identifying and recognizing spoken words, environmental sounds, and music; discriminating speech parts; and localizing sounds. These tests are critical for determining whether the patients are deaf, and, if not, what auditory information they process and experience. We gave such a battery of behavioral tests to M.L. so that we could learn about her subjective experience of sounds and compare her to other patients with auditory agnosia.

We designed and performed six tests to evaluate M.L.'s auditory perception: an auditory identification and recognition test, two-sound fusion test, two-box fusion visual control test, dichotic listening task, sound localization task, and phoneme discrimination task. We presented all the tests on a standard LG personal computer using Microsoft Windows 7 (Microsoft Corporation, Redmond, Washington). We used presentation software (Neurobehavioral Systems, Berkeley, California; www.neurobs.com) to program and administer the experiments. We delivered auditory stimuli through headphones and visual stimuli via a

computer monitor. M.L. made manual responses using the arrow keys of the computer keyboard. Before each test, the examiner invited M.L. to adjust the sound volume to her most comfortable level.

We tested M.L. over a period of 2 years. We also tested three control participants, two women and one man, with a mean age of 23. These controls, a separate group from the controls who took part in the fMRI studies, had been recruited from Bangor University's MSc psychology program. The controls found the auditory perception tests easy and scored perfectly on all of them.

This research was approved by the Ethics Committees of both the School of Psychology, Bangor University, and the National Health Service, United Kingdom. M.L. and control participants provided written consent that conformed to standards of the Declaration of Helsinki.

Auditory Identification and Recognition

In the first test, we examined M.L.'s comprehension of sounds. We presented her with 15 spoken words and 15 environmental sounds. We explained to her that she would hear each of the sounds through the headphones. Immediately after hearing each sound, she was to type what she had just heard, as best she could. Once she stopped typing, four possible answers would appear vertically aligned on the screen, and she was to choose the answer that matched the sound. In the spoken word recognition segment of the test, the four matches offered were the correct answer, a phonological distractor (eg, for the target word *glue*, the distractor was *blue*), a semantic distractor (eg, for the target word *table*, the distractor was *chair*), and a word that was neither semantically nor phonologically related to the spoken word (eg, for the target word *train*, the distractor was *hammer*).

As shown in Tables 2 and 3, immediately after listening to the sounds, M.L. was able to type correctly (sound identification) only two of the 15 words and three of the 15 environmental sounds. She performed significantly better on the second part of the test, the four-alternative forced-choice test (sound recognition). Here she made only four errors (all phonological) on the 15 words and four errors on the 15 environmental sounds.

In each trial of sound identification, M.L. required $2 \text{ (mean)} \pm 1.8 \text{ (standard deviation)}$ repetitions when she heard a spoken word and 2 ± 2.1 repetitions when she heard an environmental sound. In the sound recognition test, she required 59 ± 22 seconds to choose one of the four written options when she heard spoken words and 63 ± 22 seconds to choose when she heard environmental sounds.

Auditory Temporal Resolution: Two-Sound Fusion Test

A common finding in auditory agnosia is a tendency to perceive two short sounds (clicks or tone pips), presented with an intervening short gap (<150 to 300 msec), as though they were a single sound (Albert and Bear, 1974; Auerbach et al, 1982; Best and Howard, 1994; Buchtel and Stewart, 1989; Godefroy et al, 1995; Motomura et al, 1986; Otsuki et al, 1998; Tanaka et al, 1987; Wang et al,

TABLE 2. Patient M.L.'s Perception of Spoken Words

Word Heard	Typed Response	Multiple Choice Response
Book	Tuckin	Cook
Lake	Achoo	Lake
Glue	Bee	Blue
Table	Sneeze	Table
Rope	Bless-you	Rope
Shirt	Shout	Shirt
Pen	Slam	Pen
Lips	Gates	Hips
Carpet	Go	Puppet
House	Cards	House
Soap	Sea	Soap
Car	Car	Car
Train	Turn	Train
Radio	Radio	Radio
Stone	Sound	Stone

Correct responses are shown in **bold type**.

2000; Wolmetz et al, 2011; Yaqub et al, 1988). We used this test to measure auditory temporal resolution in M.L. and the three control volunteers.

Through the headphones (binaural presentation), we played two 2-kHz 30-msec tone pips (beeps), one after the other (60 trials). In 30 of the trials, we presented the pairs of pips with no gap. In the other 30 trials, we inserted a gap between the pips at different intervals (10 to 300 msec in 10-msec increments). We presented the 60

trials randomly. In each trial, participants were to press a button on the left if they heard two sounds, or a button on the right if they heard one sound.

All three controls had a perfect score, ie, they showed no difficulty recognizing a ≥ 10 -msec gap between the pips. By contrast, M.L. consistently perceived the two tones as a single sound for intervals of up to 100 msec. For stimulus intervals between 100 msec and 160 msec, M.L. reported hearing two sounds in half the trials. She could reliably report two pips only for intervals of ≥ 170 msec.

Two-Box Fusion Visual Control Test

Best and Howard (1994) suggested that auditory agnosia resulted from impairment in the perception of time. As perception of somatosensory and visual stimuli depends more on spatial information than on auditory stimuli, and less on temporal information, a deficit in time perception would be noticeable only for auditory stimuli. The authors provided support for this conclusion by showing that their patient with mild auditory agnosia had a temporal discrimination deficit for both auditory and visual stimuli. Tanaka et al (1987) had reported the same finding. Therefore, we also tested M.L.'s temporal resolution for visual stimuli.

In a task similar to that of Best and Howard (1994), we showed M.L. and controls two black boxes (5.3×5.3 cm) in succession, in the center of the computer screen, each for 200 msec (60 trials). In half the trials, we presented the stimuli with no intervening gap. In the other half, we inserted a gap of 17 to 300 msec in 17-msec increments. We presented the trials in random order.

Like the controls, M.L. got all 60 trials correct. She could reliably detect temporal gaps in the visual domain as brief as 17 msec.

These results demonstrate that the primary impairment in auditory agnosia is with the ability to discriminate sounds based on temporal parameters. Ilmberger (1984) had reported a similar finding of auditory, but not visual, temporal discrimination deficits in patients with aphasia.

Dichotic Listening Task

Brain-damaged patients with hearing deficits have been found to have an impaired ability to perceive sounds coming into one ear when different sounds are presented simultaneously to both ears. This phenomenon is known as *auditory extinction* or *hemi-anacusis* (Heilman and Valenstein, 1972). Many patients diagnosed with this symptom suffer from unilateral cortical damage that is contralesional to the extinguishing ear (Bellmann et al, 2001; De Renzi et al, 1984, 1989; Dumahel and Poncet, 1986; Lapras et al, 1994, on tectal damage; Michel and Péronnet, 1982). Though separate from auditory agnosia, auditory extinction has also been reported in patients with mild symptoms of auditory agnosia: left hemispheric damage with right ear extinction (Eustache et al, 1990; Pasquier et al, 1991; Stefanatos et al, 2007) and right hemispheric damage with left ear extinction (Eustache et al, 1990; Fujii et al, 1990; Mendez, 2001). Testing simultaneous sounds could thus help us determine

TABLE 3. Patient M.L.'s Perception of Environmental Sounds

Sound Heard	Typed Response	Multiple Choice Response
Telephone	Telephone	Telephone
Fire truck	Laughing	Machine gun
Car horn	Bell	Car horn
Car engine	Saw	Car brakes
Trumpet	Smashing	Trumpet
Donkey	Singing	Donkey
Dog	Barking	Dog
Owl	Space	Monkey
Rooster	Cockerel	Rooster
Toilet	Rustling	Toilet
Cat	Beep	Owl
Crow	Horn	Crow
Horse	Crying	Horse
Bird	Chimes	Bird
Rifle	Splash	Rifle

Correct responses are shown in **bold type**.

which hemisphere was predominantly responsible for M.L.'s auditory perceptual deficit and which hemisphere was able to process her remaining auditory capacities.

For M.L.'s dichotic test, we chose words from a list of six words: *money*, *couch*, *radio*, *cigar*, *flute*, and *pants*. We presented a different combination of two of the six words simultaneously to her through the headphones, each word to a different ear. Meanwhile, all six alternatives appeared on the screen. We asked her to click on all the words that she heard. We presented the six words in all 30 possible combinations. We gave her the test three times.

In all 90 trials, M.L. insisted that she heard only one word. In 68 of the trials (75.6%), she correctly identified the word presented to her left ear. In only 15 trials (16.7%) did she correctly perceive the word presented to her right ear. In the remaining seven trials (7.7%), she did not choose the correct word from either ear.

Sound Localization Task

Some patients with auditory agnosia have been reported to have a deficit in sound localization (Albert and Bear, 1974; Chocholle et al, 1975; Coslett et al, 1984; Goldstein et al, 1975; Jerger et al, 1969; Kazui et al, 1990; Lechevalier et al, 1984; Lhermitte et al, 1971; Michel et al, 1980; Tabira et al, 1981; Tanaka et al, 1965; Woods et al, 1984; Wortis and Pfeffer, 1948). Other patients have been reported not to have a sound localization deficit (Denes and Semenza, 1975; Fujii et al, 1990; Gazzaniga et al, 1973; Jerger et al, 1972; Kanschepolsky et al, 1973; Okada et al, 1963; Spreen et al, 1965).

To determine whether M.L. has such a deficit, we tested her and the controls with a similar sound localization test. In this test, each participant sat blindfolded in a rectangular room while holding a red-light laser pointer. The experimenter silently walked around the room to seven predefined locations, each at a distance of 2 meters from the participant and at a predefined angle (0, 30, 60, and 90 degrees in both auditory fields). At each of these locations, the experimenter used a clicker toy to produce a click-like sound lasting about 100 msec. Before starting the experiment, we had verified that M.L. and the controls could hear the sound and point to it accurately with their eyes open.

The participants were instructed to aim their laser pointer at the place where they heard the sound. After each trial, the experimenter placed a sticky note on the wall where the participant had pointed. Each sticky note was marked with the trial number and true stimulus location. We presented the 90 trials in randomized order. M.L., however, decided to end the experiment after only 36 trials.

All three controls consistently pointed correctly to the azimuth of the sound, with an error range that did not exceed 25 degrees. M.L., however, perceived most sounds from both auditory hemifields as being located in the left hemifield at 30 to 60 degrees from the midline (Figure 3). Thus, she mislocalized stimuli from the right hemispace as originating in the left hemispace. Moreover, compared to the controls, her localization was poor, even in the left hemispace. Within

the left hemisphere, her localization was compressed to a narrow range of between 30 and 60 degrees.

M.L.'s difficulty localizing the click-like sounds explains why she stopped the experiment early. Midway through the test, she removed her blindfold and asked us why we were presenting sounds only from the left side of the room. This acknowledgment of the absence of sounds originating in right hemisphere suggests that her localization impairment did not result from neglect of a representation of the right side of auditory space, but was caused by impaired sound localization.

Phoneme Discrimination Task

Humans' ability to produce a rich repertoire of *phonemes*—vocalizations for the purpose of speech—arises from at least two types of physical manipulation of the vocal apparatus. Manipulation of the tongue, lips, and jaw obstructs the air emerging from the lungs in different ways, thus enabling different phonemes. The unique orientation of these structures for producing an individual phoneme is known as the phoneme's *place of articulation*. Phonemes with identical places of articulation can be further diversified by timing the closure of the vocal folds before or after the obstruction of the exiting air, thus producing voiced or unvoiced phonemes, respectively. This feature of phonemes is known as *voice onset time*.

As speech comprehension requires analyzing the features of both place of articulation and voice onset time, patients with impaired speech comprehension may be more impaired at perceiving place of articulation or voice onset time, or they may be equally impaired at both. In some patients with auditory agnosia, the primary deficit has been analysis of voice onset time (Oppenheimer and Newcombe, 1978; Praamstra et al, 1991; Saffran et al, 1976), and, in others, place of articulation (Miceli, 1982; Pan et al, 2004, on inferior colliculus damage; Yaqub et al, 1988).

Because M.L.'s sound recognition test and dichotic listening test had shown us that she had partially preserved ability to perceive speech, we tested whether her perception was based primarily on analyzing the place of articulation or voice onset time features of spoken words. During each trial of this phoneme discrimination task, she heard one of eight possible words pronounced by a female English speaker: *duck*, *tuck*, *puck*, *buck*, *pier*, *beer*, *gear*, or *tear* (pronounced "teer"). After each word was presented, two written alternatives appeared onscreen, one above the other. M.L. was instructed to choose the word that she had just heard by pressing on its corresponding button. In all trials, one of the two written words was the word that she had heard; the other word was similar, but differed, with equal probability, in place of articulation, eg, *duck-buck*; voice onset time, eg, *peer-beer*; or both, eg, *duck-puck*. We gave her 13 blocks of 36 trials each, broken over several sessions that took several months.

M.L. responded with 62% accuracy when the distractor word differed by voice onset time only, 73% accuracy when the distractor word differed by place of

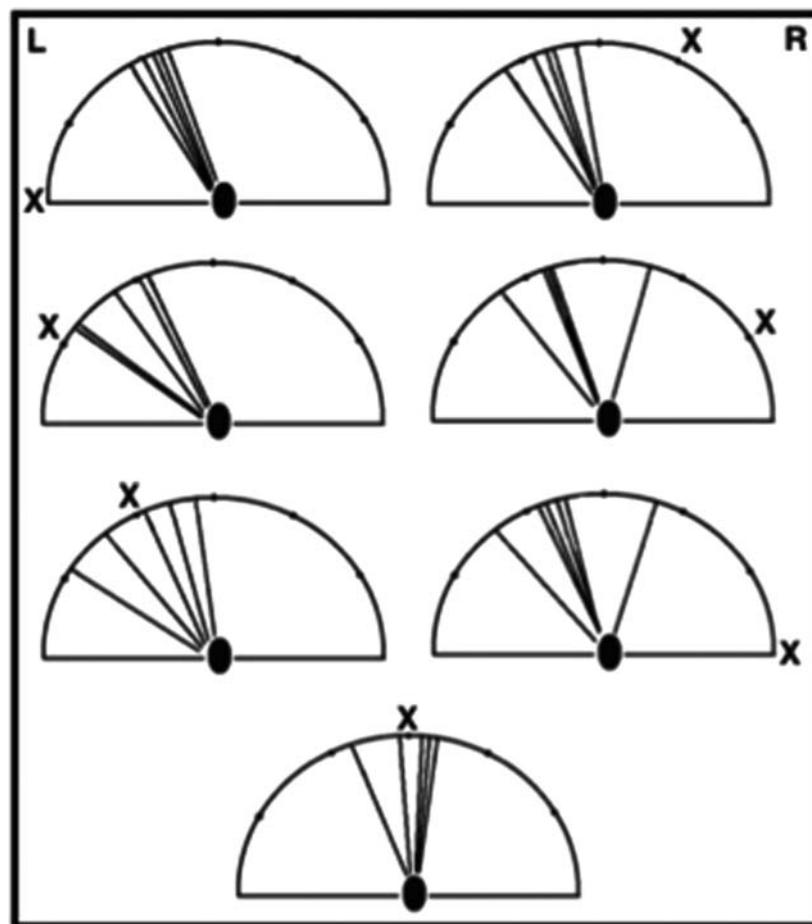


FIGURE 3. M.L.'s sound localization errors at age 27. In each half-circle, the black oval represents M.L., X represents the location of the sound presented to her, and the lines represent her perceived azimuth of the sound. L=left. R=right.

articulation only, and 78% accuracy when the distractor word differed by both place of articulation and voice onset time. Her accuracy in all three conditions was better than chance: $\chi^2 P < 0.05$ in all conditions.

A direct comparison of trials in which only voice onset time differed and trials in which both place of articulation and voice onset time differed showed that her accuracy was significantly higher when both differed: $\chi^2_{1,308} = 8.9$, $P < 0.005$. That is, she performed significantly better when information from place of articulation was available than when it was not. In contrast, her accuracy for trials in which only place of articulation differed was much the same as trials in which both place of articulation and voice onset time differed: $\chi^2_{1,308} = 0.86$, $P = 0.21$. Thus, her performance was the same regardless of the availability of voice onset time information.

Furthermore, her accuracy for trials in which only voice onset time differed was significantly lower than her accuracy for trials in which only place of articulation differed: $\chi^2_{1,308} = 4.3$, $P < 0.05$.

Overall, these results demonstrate that M.L. was less able to identify words with phonemes differing in voice onset time than phonemes differing in place of articulation.

AGE 28: fMRI INVESTIGATION

Auditory agnosia usually results from bilateral damage to the auditory cortices (Poeppel, 2001). In most patients, the syndrome appears not after a first stroke, but only after a second stroke, which may follow the first one by years (Ulrich, 1978). Because (1) bilateral lesions tend to be extensive, (2) the cortex is known to reorganize after suffering an insult, and (3) the auditory fields are small, no specific auditory field has been associated with auditory agnosia (Phillips and Farmer, 1990; Poeppel, 2001).

Given the sparing of the cortex (including both auditory cortices) in M.L. and the acute onset of her symptoms, she gave us a rare opportunity to identify the dysfunctional auditory fields in auditory agnosia. We did this with an fMRI study comparing the activation pattern in her auditory cortices when sounds were presented to her versus when she heard only scanner noise. Then we contrasted her activation pattern with those of healthy individuals.

Methods

Participants

We scanned M.L. and four neurologically healthy control participants (three women, one man) of similar age

(21 to 33 years). These controls, recruited from Bangor University's psychology program, were different from the controls who took part in the auditory perception testing and those in the initial probabilistic tractography analysis.

This research was approved by the Ethics Committees of both the School of Psychology, Bangor University, and the National Health Service, United Kingdom. M.L. and the healthy participants provided written consent that conformed with standards of the Declaration of Helsinki.

Design and Procedure

During the fMRI scan, we presented auditory stimuli to the participants in 80 blocks, with each block lasting 8 seconds and an inter-block interval lasting 2 seconds (ie, block design paradigm). Each block consisted of six to eight different stimuli. We used four types of blocks: blocks of spoken words, blocks of human vocalizations, blocks of environmental sounds, and blocks of silence (20 blocks of each type). This task was a modified version of the voice localizer used in Belin et al (2000), with the addition of blocks of single words uttered by a variety of speakers. We selected the stimuli from sounds common in daily life, and normalized them for energy (root mean square).

We instructed the participants to listen passively to the sounds with their eyes closed. We presented the sounds binaurally at an intensity of 85 dB sound pressure level (C weighting) via the electrostatic NordicNeuroLab headphone system (NordicNeuroLab Inc, Bergen, Norway) with passive noise attenuation of 30 dB at 1 kHz. We covered the headphones with foam cushions to attenuate the scanner noise further and to resist movement.

Imaging Protocol

We used a 3T Philips Achieva scanner (Philips Healthcare, Best, The Netherlands) with an eight-channel head coil and SofTone (Philips Healthcare) to reduce gradient acoustic noise by ~15 dB. We acquired continuous T2-weighted functional echoplanar imaging scans with an interleaved ascending sequence consisting of 36 slices of 3-mm thickness (0.3-mm gap) with an in-plane resolution of $2.88 \times 2.88 \times 3$ mm (field of view = 230 mm). The experimental run (repetition time = 2 seconds; echo time = 30 msec; flip angle = 90 degrees) consisted of 410 volumes (10 volumes at the end of the scan were additional silence).

At the end of the functional run, we performed whole-brain T1-weighted anatomic scans (voxel size = 1 mm^3 ; field of view = 224 mm; repetition time = 12 msec; echo time = 3.5 msec; flip angle = 8 degrees).

Analysis and Mapping of Activation in Auditory Fields

We first analyzed our data with Statistical Parametric Mapping 8 (SPM8) software (Wellcome Trust Centre for Neuroimaging, University College London, United Kingdom; <http://www.fil.ion.ucl.ac.uk/spm/>). Preprocessing of the data followed a standard analysis pipeline consisting of anterior commissure–posterior commissure alignment of the anatomic images (and application of the orientation change to all functional

images acquired in the same session). We corrected the functional scans for head motion (trilinear interpolation) by aligning all scans to the first scan of the functional run and creating a mean image. We co-registered the anatomic scan to the mean image. We generated statistical parametric maps of the *t* statistic to identify voxels that were significantly activated during the presentation of all experimental sounds (speech, human vocalizations, and environmental sounds) versus silence.

Results of whole brain analyses are illustrated at a cluster height threshold (*T*) of 3.11 voxels and a cluster extent threshold (kE) of 10 voxels. Significant clusters are reported at *P* < 0.001, family wise error-corrected at the cluster level.

We conducted further analyses with the FSL fMRI Expert Analysis Tool (FEAT) (Analysis Group, FMRIB, Oxford, United Kingdom; <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki>).

Results

To visualize the blood-oxygen-level-dependent (BOLD) activation in relation to auditory fields on the supratemporal plane, we manually erased the parietal and frontal lobes using the FSLView toolbox and rendered them into three-dimensional space with MRICroGL (hosted by the McCausland Center for Brain Imaging, University of South Carolina, Columbia, South Carolina; <http://www.cbiatl.com/mricrogl>), thus exposing the temporal operculi. Following the method of Viceic et al (2009), we co-registered these images with maps of human auditory fields identified in postmortem brains with cytochrome oxidase staining (Wallace et al, 2002).

Figures 4 and 5 show several features that confirm the placement of Wallace et al's map of auditory areas on our participants' auditory cortices. For instance, the external contours of the temporal lobe in all participants closely matched the external contours of the temporal lobe in the map. Moreover, M.L.'s BOLD activation clusters corresponded well with the location of the auditory fields in the map. In particular, the location of M.L.'s Heschl gyrus closely matched the location of Heschl gyrus in Wallace's map, and the parcellation in Wallace's map of Heschl gyrus into posterior and anterior parts (corresponding to areas hA1 and hR, respectively) matched with activation in M.L.'s posterior, but not anterior, Heschl gyrus in the left hemisphere.

In the right hemisphere, M.L. has a forked (bifid) Heschl gyrus that prevented the matching of her activation to the Wallace map. However, a recent fMRI study that localized hA1 and hR in different individual Heschl gyrus topographies showed that a sulcus bisecting Heschl gyrus is the landmark separating hA1 and hR (Da Costa et al, 2011). In M.L.'s right hemisphere, activation in Heschl gyrus was restricted to the region posterior to the bisecting sulcus.

In all four controls (Figure 6), activation was spread bilaterally across the supratemporal plane, superior temporal gyrus (STG), and superior temporal sulcus, and in varying locations in the frontal lobes (primarily Broca

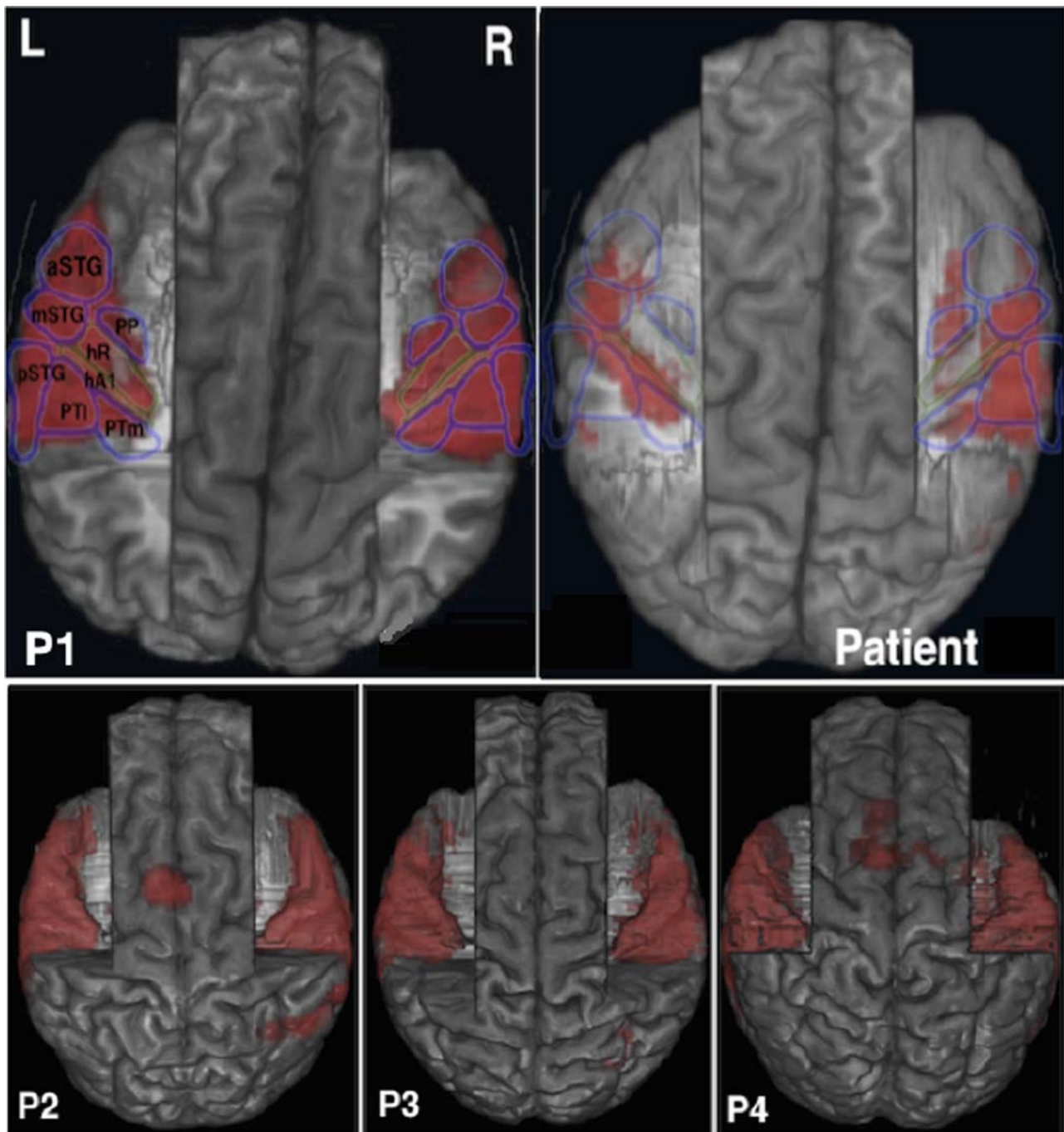


FIGURE 4. M.L. at age 28, compared with controls on a functional magnetic resonance imaging scan during a passive listening task. Shown from above are three-dimensional renderings of T1-weighted images with superimposed blood-oxygen-level-dependent (BOLD) activation in red. Top right panel: M.L. Top left and three bottom panels: four healthy age-matched control participants, labeled P1 to P4. To demarcate the auditory fields, we superimposed a map of the auditory cortex (Wallace et al, 2002) on the top left image of a representative control and on the top right image of M.L. (We changed the labels of the auditory fields from those of Wallace et al [2002] to more common terminology.) In contrast to the controls, M.L.'s activation was limited to the hA1 (bilateral), middle STG (bilateral), PP (right), posterior STG (right), and planum temporale (both PTl and PTm) (right) fields. **aSTG**=anterior superior temporal gyrus. **hA1**=human primary field A1 (ie, Heschl sulcus or posterior Heschl gyrus). **hR**=human primary rostral field (ie, anterior Heschl gyrus). **mSTG**=middle superior temporal gyrus. **PP**=planum polare. **PTl**=lateral planum temporale. **PTm**=medial planum temporale. **pSTG**=posterior superior temporal gyrus.

area and dorsal premotor cortex). Two control participants also showed activation in the left parietal lobe.

M.L.'s pattern of activation in the auditory cortex was more limited than the controls' (Figures 4 and 5). In her left hemisphere, the significant cluster ($T = 5.93$; $kE = 235$) covered Heschl sulcus (which is area hA1 according to Humphries et al, 2010; Langers and van Dijk, 2012; and Striem-Amit et al, 2011), while the remaining Heschl gyrus (which is area hR according to the same citations) was not activated. In the associative auditory cortices of both hemispheres, we found activation in the middle STG (area PaAr of Engelien et al, 2002, and Fullerton and Pandya, 2007; area 1.2 of Morosan et al, 2001; area ALA of Wallace et al, 2002).

In M.L.'s right hemisphere, we also found activation ($T = 8.4$; $kE = 314$) in the planum temporale (area PaAc of Fullerton and Pandya, 2007; areas PA and LA of Rivier and Clarke, 1997, and Wallace et al, 2002; parabelt region of Sweet et al, 2005; Westbury et al, 1999), posterior STG (area PLST of Howard et al, 2000, and Steinschneider et al, 2011; area STA of Rivier and Clarke, 1997, and Wallace et al, 2002), and planum polare (area MA of Rivier and Clarke, 1997, and Wallace et al, 2002; area PaI of Fullerton and Pandya, 2007).

When compared with the controls' areas of activation, several of M.L.'s auditory fields were nonreactive to sounds: the anterior STG bilaterally (area Ts2i of Fullerton and Pandya, 2007; area AA of Wallace et al, 2002) and, in the left hemisphere, the planum polare and the posterior auditory fields (planum temporale and posterior STG).

In contrast to the controls, M.L.'s data obtained outside the supratemporal plane and STG revealed bilateral nonreactivity of the superior temporal sulci and frontal lobes (Figure 5). Small areas of activation were seen in her left temporoparietal junction, right intraparietal sulcus, and left cerebellum. Similar parietal activation was also seen in control participants P3 and P4, and similar cerebellar activation in P2 and P4 (Figure 6).

DISCUSSION

Patient M.L.'s auditory agnosia resulted from a traumatic brain injury that caused a partial interruption of the auditory pathways in her brainstem. She had a severe reduction in auditory temporal resolution. While she could not identify isolated words or environmental sounds, her auditory perception was remarkably facilitated by contextual cues, especially when a sound was presented to her with written alternatives.

Even under forced-choice conditions, however, M.L. had particular difficulty in differentiating sounds that could be distinguished only by acoustic similarity: She was particularly impaired in discriminating syllables that differed in voice onset time and, to a lesser extent, in place of articulation. Further, under dichotic listening conditions, M.L. demonstrated extinction of sounds presented to her right ear (hemi-anacusis), contralesional to her damaged left inferior colliculus. She also had poor sound localization, with the location of sounds presented on the right of midline shifting to left hemispace.

As with other patients who have auditory agnosia, M.L.'s speech comprehension was dramatically enabled by concomitant lipreading and contextual cues.

Comparison of M.L. with Previous Patients with Inferior Colliculus Lesions

In Supplemental Digital Content 1, <http://links.lww.com/CBN/A63>, we list 51 published case reports of patients with collicular lesions and summarize their auditory deficits. Unilateral left or right inferior colliculus lesions resulted in either mild or transient auditory disturbances that were restricted to the contralesional hemifield. All cases of bilateral inferior colliculus damage resulted in either severe auditory agnosia or complete deafness.

M.L.'s MRI scans suggest that her condition could be unique, as no anatomic damage was seen in her right inferior colliculus or elsewhere in the auditory pathway of her right hemisphere.

Even so, her brainstem evoked potentials revealed impaired processing in both inferior colliculi because wave V, which is generated in the inferior colliculus contralateral to the stimulated ear (Allen and Starr, 1978; Fischer et al, 1994; Hashimoto et al, 1981; Stockard and Rossiter, 1977), was abnormal after sounds were presented to either her right or left ear: Wave V was delayed after presentation to the left ear, and absent after presentation to the right ear.

Since M.L.'s brain damage was caused by severe head trauma, her brain injury (especially axonal shearing) is presumably more extensive than was visualized with MRI. For example, the oculomotor signs clearly suggest dysfunction in the pretectum. It therefore seems probable that the brainstem contusion damaged both her right and left inferior colliculi, with almost complete destruction of the left. This conclusion is further corroborated by the reduction of the BOLD signal in both auditory cortices, but more severe in the left hemisphere.

M.L.'s BOLD Activation Pattern Shows Segregation into Ventral and Dorsal Auditory Streams in the Primary Auditory Cortex

Over the past two decades, several comparative models have described a functional dichotomy in the auditory cortex (summarized in Figure 7) (Clarke and Thiran, 2004; Hickok and Poeppel, 2007; Rauschecker and Scott, 2009; Rauschecker and Tian, 2000; Romanski et al, 1999; Scott and Wise, 2004; Ueno et al, 2011; Zatorre et al, 2002). These models describe a bilateral auditory ventral pathway with hierarchical processing from the anterior STG to the superior temporal sulcus and middle temporal gyrus, which are posited to be responsible for the analysis of speech properties (eg, voicing) and further recognition of spoken words and other sounds.

These models also describe a parallel left dominant auditory dorsal pathway with hierarchical processing from the posterior STG to the inferior parietal cortex (see also Brunetti et al, 2005; Edwards et al, 2010), which has been shown to be involved in a variety of functions, such as audiospatial processing (Clarke and Thiran, 2004;

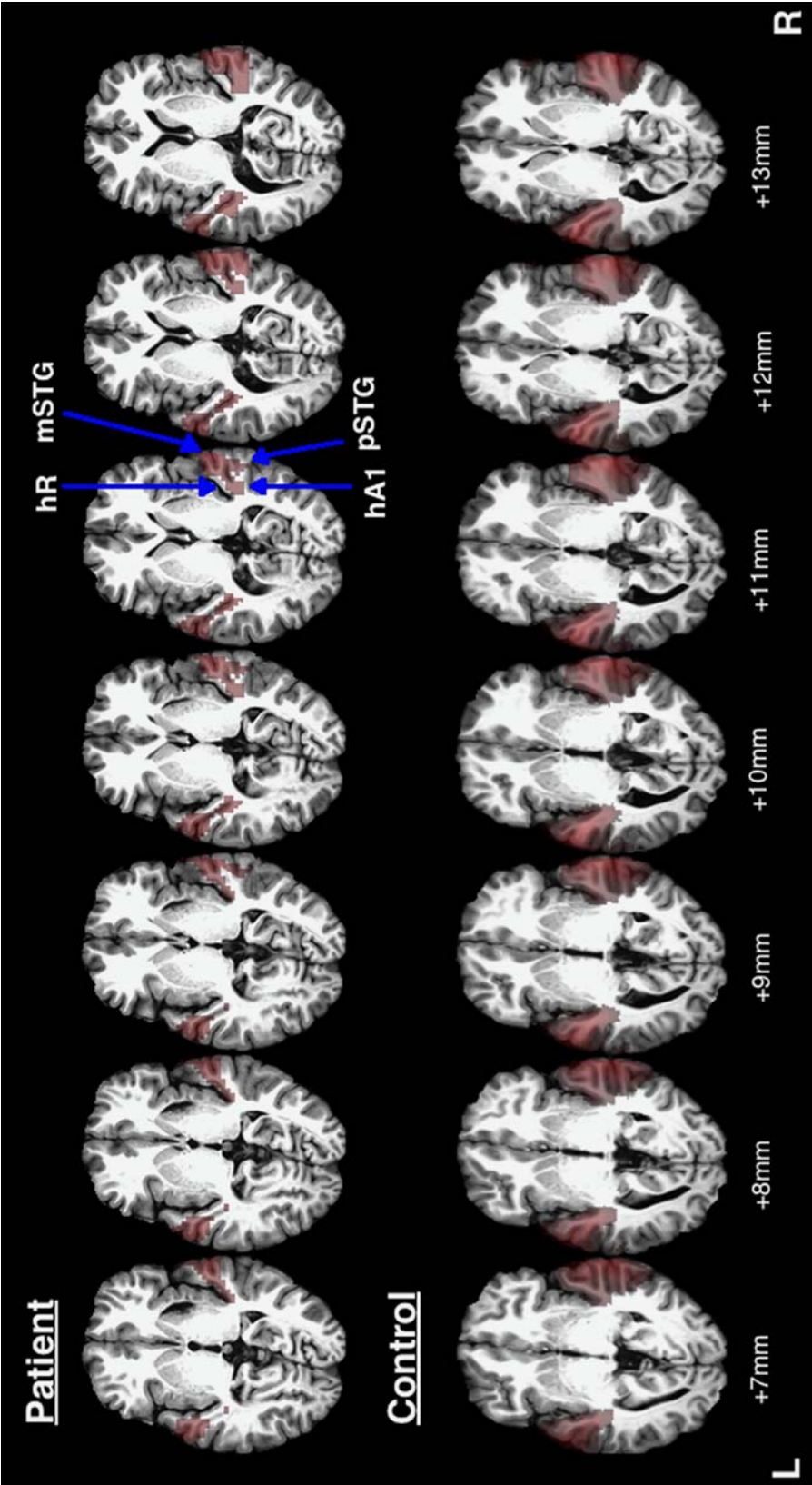


FIGURE 5. A series of axial T1-weighted functional magnetic resonance images from M.L. (top) and a representative control participant, P1 (bottom), during the passive listening task. Both images have superimposed blood-oxygen-level-dependent (BOLD) activation. In contrast to the controls, M.L.'s activation was restricted bilaterally to Heschl sulci (posterior Heschl gyri) (hA1), with no activation in the anterior Heschl gyri (hR). The numbers at the bottom of the figure represent the distance (millimeters) of the axial scan from the anterior commissure-posterior commissure plane. **mSTG**=middle superior temporal gyrus. **pSTG**=posterior superior temporal gyrus.

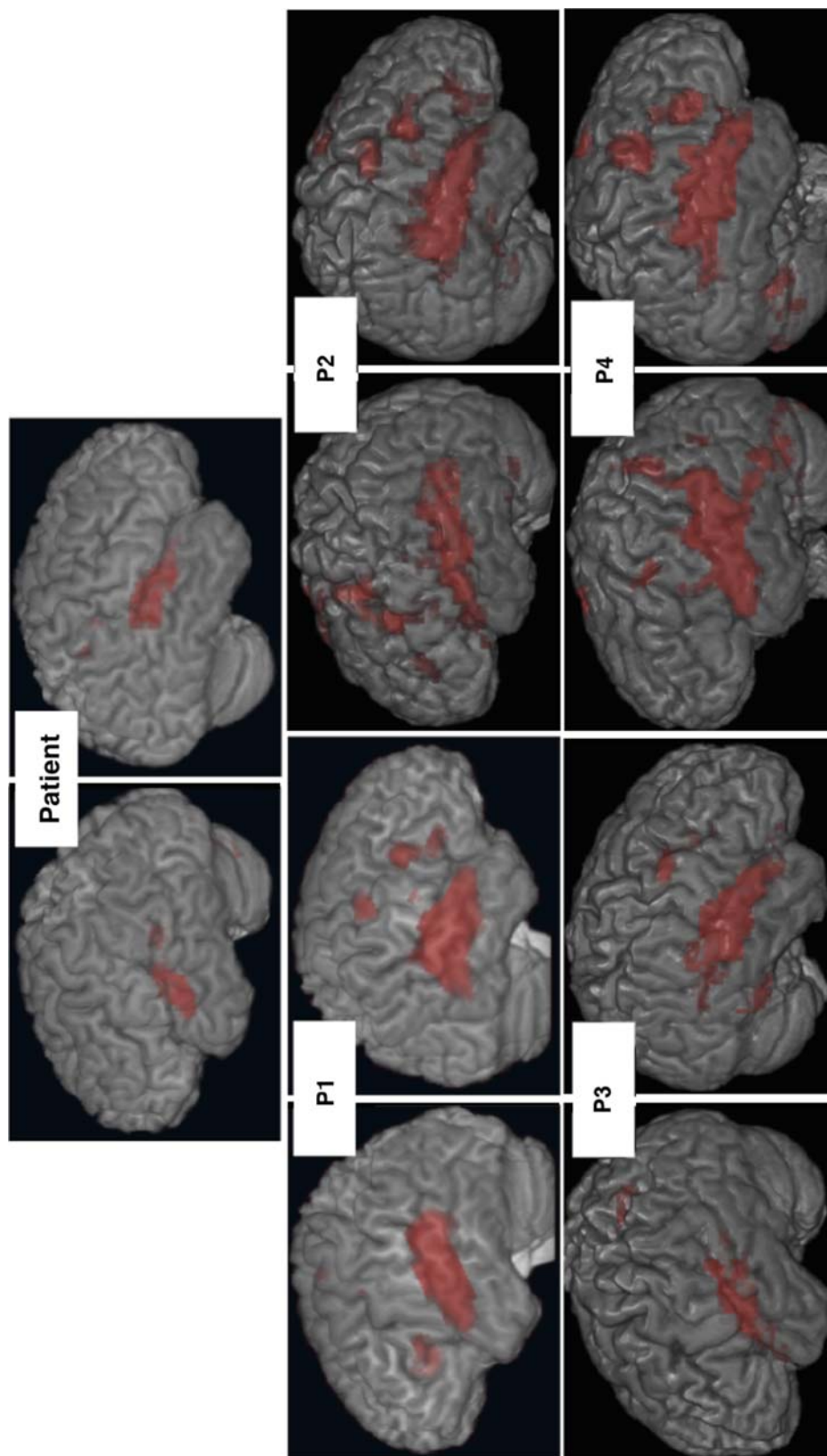


FIGURE 6. Three-dimensional renderings of the T1-weighted functional magnetic resonance imaging scans, with superimposed blood-oxygen-level-dependent (BOLD) activation, for M.L. and the four healthy controls, P1 to P4. All four controls showed activation in the superior temporal gyrus, superior temporal sulcus, and frontal lobe. Two controls (P3 and P4) also had activation in the parietal lobe, and two (P2 and P4) in the cerebellum. M.L. had limited activation in the superior temporal gyrus, with small regions of activation in the left temporoparietal junction, right intraparietal sulcus, and left cerebellum. In contrast to the controls, M.L. had no activation in her superior temporal sulci or frontal lobes.

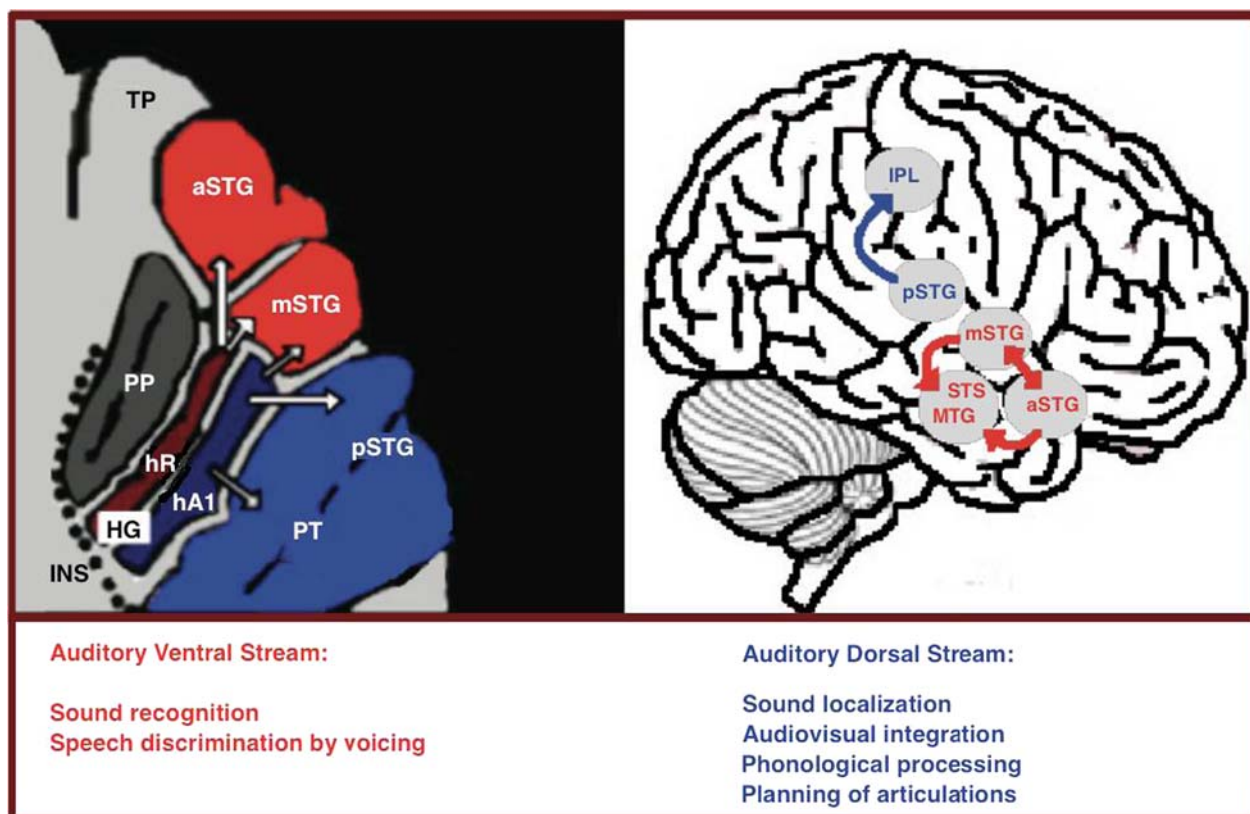


FIGURE 7. A schematic representation of the human auditory cortex and its immediate connections: views of the supratemporal plane from above (left) and the side (right). We based our diagram on the demonstration of histologic staining of postmortem brains by Wallace et al (2002). In accordance with contemporary models, the auditory cortex is divided into two processing streams. The auditory dorsal stream (blue regions) is postulated to be responsible for sound localization, audiovisual integration, phonological processing, and planning of articulations. The auditory ventral stream (red regions) is associated with sound recognition in general and the identification of speech features (eg, detection of voicing in phonemes) in particular. Our fMRI findings indicate that this dissociation into ventral and dorsal streams occurs earlier than previously assumed, with hR being an early ventral stream region, and hA1 an early dorsal stream region. aSTG = anterior superior temporal gyrus. hA1 = Heschl sulcus or posterior Heschl gyrus. HG = Heschl gyrus. hR = anterior Heschl gyrus. INS = insula. IPL = inferior parietal lobule. mSTG = middle superior temporal gyrus. MTG = middle temporal gyrus. PP = planum polare. pSTG = posterior superior temporal gyrus. PT = planum temporale. STS = superior temporal sulcus. TP = temporal pole.

Rauschecker and Tian, 2000), audiovisual integration (Campbell, 2008; Kayser et al, 2009; Mazzone et al, 1996), sensorimotor transformation during speech repetition (Hickok and Poeppel, 2007; Rauschecker and Scott, 2009), phonological working memory (Buchsbaum et al, 2011), and phonological manipulations of words (Gow, 2012).

As we will show in the next several sections, when combined with evidence from previous literature, M.L.'s auditory fMRI and behavioral data support the key features of the model shown in Figure 7. We also provide novel findings that could potentially advance our understanding of the pathophysiology of auditory agnosia and the functional fractionation of the auditory cortex.

M.L.'s Auditory Agnosia Is Caused by Bilateral Dysfunction of the Auditory Ventral Stream

Previous studies have examined the role of the anterior STG (Davis and Johnsrude, 2003; DeWitt and

Rauschecker, 2012; Lachaux et al, 2007; Matsumoto et al, 2011; Obleser et al, 2006a, 2008) and anterior superior temporal sulcus (Belin and Zatorre, 2003; Bestelmeyer et al, 2011) in sound recognition using functional imaging, intracortical recording (electrocorticography), and transcranial magnetic stimulation. On the basis of these studies and literature documenting that auditory agnosia for both verbal and environmental sounds results most often from bilateral temporal damage, Hickok and Poeppel (2007) hypothesized that auditory agnosia is caused by bilateral disruption of the auditory ventral stream.

Heffner and Heffner (1986) had earlier provided evidence for this hypothesis in monkeys by showing that monkeys with bilateral, but not unilateral, superior temporal lobe lesions were impaired at recognizing specific calls. These researchers also showed that monkeys continued to recognize acoustic patterns after their auditory cortex was removed unilaterally, but they lost the ability

after a second lesion was induced to the anterior, but not posterior, STG. This study thus localized auditory agnosia to the auditory ventral stream (Harrington and Heffner, 2002).

In M.L.'s case, neither the anterior STG nor the superior temporal sulcus responded to sounds. Her activation pattern provides evidence that auditory agnosia in humans is associated with bilateral disruption to the auditory ventral stream.

M.L.'s BOLD Activation Pattern Converges with Other Evidence That Primary Area hR Projects to the Anterior STG and Primary Area hA1 Projects to the Middle and Posterior STG

Histologic staining and tracing studies in monkeys have demonstrated two auditory fields that receive afferents from the medial geniculate body, ie, two primary auditory fields: an anterior auditory field, area R, and a posterior auditory field, area A1 (Hackett et al, 2001; Morel and Kaas, 1992; de la Mothe et al, 2006). Morel and Kaas (1992) also suggested the existence of a third primary auditory field, area RT, located anterior to area R.

Studies using electrophysiological recordings and fMRI in monkeys further showed that each of these primary auditory fields has a separate tonotopic organization (Bendor and Wang, 2008; Bieser and Müller-Preuss, 1996; Kusmirek and Rauschecker, 2009; Merzenich and Brugge, 1973; Petkov et al, 2006; Recanzone et al, 2000; Woods et al, 2006; Yin et al, 2008). Downstream from the primary auditory fields, histologic tracing and lesion studies showed that monkey area A1 projects to the posterior STG, and areas R and RT project to the anterior STG (Morel et al, 1993; de la Mothe et al, 2012; Rauschecker et al, 1997).

In humans, postmortem histologic staining has revealed two primary auditory fields in the primary auditory region, ie, Heschl gyrus (Sweet et al, 2005; Wallace et al, 2002). On the basis of tonotopic mappings shown with fMRI, these primary auditory fields appear to be homologues to the monkey primary auditory fields A1 and R (Da Costa et al, 2011; Formisano et al, 2003; Humphries et al, 2010; Langers and van Dijk, 2012; Striem-Amit et al, 2011; Talavage, 2003). Studies that recorded activity from the supratemporal plane of patients with epilepsy reported activation spreading from the posterior Heschl gyrus (hA1) to the posterior STG, and from the anterior Heschl gyrus (hR) to the anterior STG (Gourévitch et al, 2008; Guéguin et al, 2007). These studies suggest similar connectivity in the auditory cortex of humans and monkeys.

Consistent with the connectivity of the human and monkey auditory cortices, we observed that M.L. had bilateral auditory activation in hA1, the middle STG, and the right posterior STG, while her hR and anterior STG were unresponsive to sounds bilaterally (Figures 4 and 5).

Thus, our observations of M.L. converge with other evidence that area hR projects to the anterior STG, and area hA1 projects to the middle STG and posterior STG (Figure 7). This connectivity is further corroborated by other human fMRI studies that reported contiguous activations along hR-anterior STG and along hA1-middle STG and

posterior STG (Brechmann et al, 2002; Di Salle et al, 2001; Hashimoto et al, 2000; Langers et al, 2007; Patterson et al, 2002; Scheich et al, 1998; Schönwiesner et al, 2002).

M.L.'s Impairment in Discriminating Phonemes by Their Voicing Is Caused by Bilateral Nonreactivity of Area hR and the Anterior STG

M.L. was more impaired in discriminating syllables differing only in voice onset time than those differing only in place of articulation. In an fMRI study, Obleser et al (2006b) associated voice onset time discrimination primarily with the ventral stream by demonstrating sensitivity to differences in voicing in the anterior STG. Similarly, voice onset time-related activation in the anterior Heschl gyrus (area hR), but not the posterior Heschl gyrus (area hA1), has been demonstrated with both intracortical recording (Steinschneider, 2004) and fMRI (Hutchison et al, 2008).

We interpret our findings as evidence for the role of areas hR and anterior STG (the ventral pathway) in the processing of voice onset time. This functional segregation between the ventral and dorsal streams at the level of the primary auditory cortex (Figure 7) is corroborated by monkey studies showing that only the rostral core (Yin et al, 2008) and belt (Harrington et al, 2001; Rauschecker et al, 1997) are responsible for sound recognition.

M.L.'s Spared Auditory Abilities Result from Relatively Intact Processing in Her Right Posterior STG

Having established that M.L.'s auditory deficits correspond to bilateral disruption of her auditory ventral stream, we now consider the mechanisms or structures underlying her preserved auditory abilities. Our findings may also shed light on the auditory abilities of patients whose auditory agnosia was caused by cortical lesions.

M.L.'s right, but not left, posterior STG was activated by sounds. As mentioned, this region is considered to be an early processing center of the auditory dorsal stream, a pathway that has been shown to be involved in sound localization, audiovisual integration (with emphasis on lipreading), and encoding of the phonological and acoustic structure of sounds into both working memory and long-term memory. Four of our findings indicate that M.L.'s spared auditory abilities reflect processing in her right auditory dorsal stream.

First, on the dichotic listening test she demonstrated auditory extinction of words presented in her right ear, thus localizing her spared auditory abilities to her right auditory cortex.

Second, on the sound localization task, she systematically mislocalized stimuli presented to her right auditory hemifield, shifting them toward the left hemifield, also reflecting processing in the right posterior STG.

Third, she appears capable of registering the phonological and acoustic structure of words. On the auditory recognition test, all four of her errors were for phonologically, but not semantically, similar words. On

another occasion, she typed to dictation the word *knock* when she heard the phonologically similar word *donkey*.

Fourth, she appears to benefit greatly from lip-speech integration.

The literature suggests that M.L.'s preserved auditory abilities may also be found in patients with auditory agnosia caused by cortical lesions. Like her, patients with cerebral auditory agnosia have been reported to be better at recognizing words when presented with choice alternatives, and to be more prone to phonological than semantic errors (Best and Howard, 1994; Buchman et al, 1986; Engelien et al, 1995; Eustache et al, 1990; Garde and Cowey, 2000; Goldstein et al, 1975; Kazui et al, 1990; Kirshner and Webb, 1981; Lechevalier et al, 1984; Maneta et al, 2001; Marshall et al, 1985; Mendez, 2001; Mendez and Geehan, 1988; Miceli, 1982; Michel et al, 1980; Pinard et al, 2002; Saffran et al, 1976; Tessier et al, 2007).

An additional similarity between M.L. and patients with cerebral auditory agnosia is the ability to integrate speech with lip movements. As far as we know, speech comprehension in all reported patients with auditory agnosia has benefited from face-to-face interactions (Auerbach et al, 1982; Buchman et al, 1986; Kirshner and Webb, 1981; Metz-Lutz and Dahl, 1984; Oppenheimer and Newcombe, 1978; Shindo et al, 1991).

Although M.L.'s auditory abilities are similar to those reported for patients with cortical auditory agnosia, we cannot compare her auditory activation pattern to those of other patients because only one other patient with auditory agnosia has undergone functional imaging—the patient who had recovered from auditory agnosia, in whom spoken words activated the right posterior STG (Engelien et al, 1995).

Experiments that modeled auditory agnosia in monkeys (Harrington and Heffner, 2002; Harrington et al, 2001) lend support to our proposal that the preserved auditory abilities of M.L. and others with auditory agnosia are explained by preserved processing in the posterior STG of the dorsal stream. In those monkey experiments, the researchers induced auditory agnosia-like symptoms after damaging the auditory cortices bilaterally while sparing the posterior STG unilaterally.

M.L. Can Perceive Auditory Objects But Cannot Register Their Acoustic Details

One factor contributing to the hearing impairments of patients with brain lesions is poor temporal resolution, which is typically measured with a two-click fusion threshold task. In a variant of this task, we presented M.L. with two 30-msec tone pips separated by varying time intervals, and found that she could consistently perceive the two pips as distinct only if the gap was ≥ 170 msec.

Severe impairments of auditory temporal resolution (100 to 300 msec) have been reported in other patients with severe auditory agnosia (Buchtel and Stewart, 1989; Godefroy et al, 1995; Motomura et al, 1986; Otsuki et al, 1998; Tanaka et al, 1987) or fluent aphasia (Carmon and Nachshon, 1971; De Renzi et al, 1989; Efron, 1963; Lackner and Teuber, 1973; Stefanatos et al, 2007).

Corroborating the relationship between sound fusion threshold and auditory agnosia are studies that tracked the recovery of patients with auditory agnosia and correlated their improvement in temporal discrimination with the resolution of their agnosic symptoms (Godefroy et al, 1995; Motomura et al, 1986).

Converging evidence suggests that 100 to 300 msec is the time required to process auditory objects. For instance, in a backward masking study, Massaro (1972) showed that a masking noise inserted between two monosyllabic words with similar vowels interfered with their discrimination only if the masking noise was shorter than 270 msec. Similarly, Wallace and Blumstein (2008) showed that speech and non-speech sounds of different durations can prime the identification of a vowel of the same duration and that this priming effect disappears for durations longer than 150 msec. In a study using electroencephalography, Yabe et al (2001) showed that sounds differing in frequency elicit a mismatch negativity response only if the inter-sound interval is ≤ 170 msec.

Interestingly, 100 to 300 msec corresponds to the duration of syllables (Greenberg, 2006; Studdert-Kennedy et al, 1970) and to the minimal required gap for perceiving syllables as separate (Repp, 1980). During a preliminary listening assessment, M.L. was able to tap on the table at the onset of each syllable she heard. These findings suggest that she and other patients with auditory agnosia are capable of segregating sounds (eg, spoken words) into discrete auditory objects (eg, syllables), but cannot discriminate the auditory objects sufficiently to permit comprehension. This account is consistent with our association of auditory agnosia to disruption of the ventral stream, as fMRI studies in healthy individuals have directly correlated anterior STG activation with the perception of auditory objects (Scheich et al, 1998; Zatorre et al, 2004).

According to Viemeister and Wakefield's (1991) "multiple looks" model, sounds are segregated not only into 100- to 300-msec units, but also into much shorter 5- to 10-msec units. The researchers presented participants with two pulse sounds separated by 100 msec of noise, and showed that removing one of the pulses increased the sound level required for detecting the remaining pulse. The researchers concluded that the auditory system segments sounds into durations of ≥ 100 msec. The investigators then repeated the task with very short quiet intervals. They showed that as the interval increased, the required sound level for detecting the second pulse sound gradually decreased, and that this effect asymptotes at 5-msec intervals. Their study thus shows that the acoustic details of each sound object are also encoded temporally.

Such a deconstruction of auditory objects into shorter units is consistent with studies reporting patients whose auditory agnosia is restricted to impaired comprehension of spoken words (pure word deafness). In these patients, temporal discrimination has been impaired for very short intervals of 15 to 50 msec (Albert and Bear, 1974; Auerbach et al, 1982; Wang et al, 2000; Wolmetz et al, 2011; Yaqub et al, 1988), which correspond to the duration of discrete consonants (Rosen, 1992). Fur-

thermore, in patients with auditory agnosia who had a specific impairment in comprehending environmental sounds but a spared perception of words, their discrimination was spared for short durations but impaired for longer durations of 50 to 200 msec (Motomura et al, 1986; see also Lambert et al, 1989, who reported a patient with an intact 10-msec tone fusion threshold).

Taken together, these findings suggest that patients with auditory agnosia, even in its most severe form, are capable of detecting auditory objects (eg, the onset of syllables), but are impaired at perceiving the acoustic details of each auditory object.

M.L.'s Atypical Features

We have reported novel observations in a patient with the very rare condition brainstem auditory agnosia. Our findings shed new light on the functional organization of the auditory cortex, and have implications for understanding the pathophysiology of auditory agnosia in patients whose hearing loss is caused by cortical damage.

Our cardinal new findings from this fractionating of M.L.'s auditory fields support a dichotomy of auditory function into ventral and dorsal streams. Our findings suggest that auditory comprehension depends on bilateral processing in the anterior STG (auditory ventral stream), and that localization, lip-speech integration, and phonological analysis depend on processing in the posterior STG (auditory dorsal stream). Consistent with the connectivity between the primary and associative auditory ventral stream and between the primary and associative auditory dorsal stream demonstrated in monkeys (Kaas and Hackett, 2000), our observations further suggest that in humans the two streams segregate as early as the primary auditory cortex.

While M.L.'s auditory agnosia shares many similarities with numerous reported cases of auditory agnosia caused by cortical lesions, we acknowledge constraints in generalizing from a single patient, especially a patient with atypical clinical features. We conclude by considering some of these limitations.

Although pure-tone audiometry suggested severe impairment in M.L.'s ability to detect sounds, we have argued that her auditory agnosia is not attributable to an elevation of auditory amplitude thresholds. Atypically for peripheral hearing loss, her audiometric thresholds for narrow-band sounds were much lower than for pure tones. Detection of narrow-band sounds is more likely than pure tones to reflect M.L.'s detection abilities for speech and environmental sounds. When tested with everyday sounds, she adjusted the volume of the headphones to levels that did not indicate that she needed amplification in order to detect the sounds. Her subjective reports of "tunes in my head" and sound distortion (hearing pure tones as sounding like "someone whistling" rather than beeps) suggest that her poor performance on pure-tone audiometry may reflect an alteration of signal-to-noise ratio rather than simply an elevation of amplitude detection threshold.

Cochlear testing confirmed normal functioning of her hair cells, and, anatomically, auditory transmission was

intact to the level of her lower brainstem, as demonstrated by normal wave I and III auditory evoked potentials.

We conclude, therefore, that her hearing impairment, including the striking asymmetry between her left and right ears, is the result of asymmetric damage in the brainstem. The neuroimaging measures showing white matter integrity of her thalamocortical connections suggest that the damage was chiefly below the level of the medial geniculate nucleus.

Although she has both crossed and uncrossed connections (from both ears) above the level of the lower pons, they remain asymmetric. Her left auditory cortex receives dominantly crossed projections from the right ear, and her right auditory cortex receives dominantly crossed projections from the left ear.

Møller et al (1995) have shown that uncrossed projections from the ipsilesional ear contribute very little to auditory potentials evoked at the level of the inferior colliculus. Unilateral lesions of the macaque monkey's auditory cortex have been reported to cause severe hearing loss in the contralesional ear (Heffner and Heffner, 1989).

However, to our knowledge, patients with unilateral damage to the auditory cortex have had only very mild pure-tone audiometry hearing loss in the contralesional ear (Saffran et al, 1976; Stefanatos et al, 2007). In one patient with unilateral damage to the inferior colliculus, brachium, and medial geniculate nucleus, pure-tone audiometry was normal in both ears (Fischer et al, 1995). Nevertheless, these patients, like ours, had extinction on dichotic listening tasks.

Thus, M.L. may be unique among people with auditory agnosia resulting from either brainstem or cortical lesions, in having such apparently asymmetric hearing loss in the ear contralateral to the dominant lesion in her left inferior colliculus. The reason for this asymmetry remains unclear, but, as noted earlier, cannot be readily explained as auditory neglect. Recall that during the localization task, M.L. commented spontaneously on the absence of sounds coming from her right side. The ear asymmetry could be construed as neglect of information from the contralesional ear, and, like the localization bias and auditory extinction during dichotic listening, may also reflect asymmetric deafferentation of the auditory dorsal stream.

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